REMARKS

Claims 1-26 were pending in this application. Claims 5, 16-19, and 22 are now canceled without prejudice to the Applicants' right to prosecute their subject matter in the present application or in related applications. New claims 27-51 are added, and claims 1-4, 6-15, 20, 21, and 23-26 are amended. Accordingly, claims 1-4, 6-15, 20, 21, and 23-51 will be pending upon entry of this amendment and presented for reconsideration.

Amendments to the Specification

Applicants have made corrections to the specification to correct typographical and grammatical errors. Applicants submit that no new matter has been introduced.

Amendments to the Claims

Support for claim amendments and new claims can be found throughout the application as filed, including the original claims. Examples of such support in the specification are described below.

Claims 1 and 3 are both amended to recite "recombinant tissue factor" instead of "tissue factor." Support for this amendment can be found, for example, at page 6, line 13 and in original claim 5.

Claims 1, 3, 4, 23, and 24 each have been amended to recite "calcium ion" instead of "calcium." Support for this amendment is discussed *infra* in connection with the 35 U.S.C. § 112 rejections.

Claim 2 is amended to depend from claim 1. Support for this amendment can be found, for example, in original claim 2.

Claim 4 is amended to depend from 3. Support for this amendment can be found, for example, in original claim 4.

Claims 6-15, 20-21, and 23-26 have been amended to claim appropriate dependencies and/or to remove parenthetical expressions and abbreviations objected to by the Examiner and to replace those abbreviations appropriately, as well as to make grammatical changes or to correct typographical errors.

Claim 24 has been amended to recite "synthetic phospholipid" instead of "phospholipid." Support for this amendment can be found, for example, at page 7, lines 7-9.

Claim 25 and 26 are both amended to recite "protein S activity" instead of "protein S." Support for this amendment can be found, for example, in original claim 25 and at page 7, lines 9-11.

Support for new claims 27-29 can be found, for example, at page 7, lines 7-11.

Support for new claim 30 can be found, for example, in original claim 24 and at page 7, lines 7-11.

Support for new claims 31 and 32 can be found, for example, in original claims 25 and 26, and at page 7, lines 7-11.

Support for new claim 33 can be found, for example, in original claims 1 and 8, and at page 6, lines 16-17.

Support for new claim 34 can be found, for example, in original claims 2 and 8.

Support for new claim 35 can be found, for example, in original claim 5, and at page 6, 16.

Support for new claim 36 can be found, for example, in original claim 6, and at page 6, line 13.

Support for new claim 37 can be found, for example, in original claim 7, and at page 7, lines 4-5.

Support for new claim 38 can be found, for example, in original claim 9, and at page 6, lines 16-20.

Support for new claim 39 can be found, for example, in original claim 10, and at page 6, lines 16- 20.

Support for new claim 40 can be found, for example, in original claim 11, and at page 8, lines 12-13.

Support for new claim 41 can be found, for example, in original claim 12, and at page 8, lines 10-12.

Support for new claim 42 can be found, for example, in original claim 13, and at page 6, line 21.

Support for new claim 43 can be found, for example, in original claim 14, and at page 7, lines 4-5.

Support for new claim 44 can be found, for example, in original claim 15, and at page 7, lines 4-5.

Support for new claim 45 can be found, for example, in original claim 20, and at page 10, lines 9-10.

Support for new claim 46 can be found, for example, in original claim 21, and at page 10, lines 9-10.

Support for new claim 47 can be found, for example, in original claim 3, and at page 6, lines 16-17.

Support for new claim 48 can be found, for example, in original claims 4 and 8.

Support for new claim 49 can be found, for example, in original claim 5, and at page 6, line 16.

Support for new claim 50 can be found, for example, in original claim 7, and at page 7, lines 4-5.

Support for new claim 51 can be found, for example, in original claim 15, and at page 7, lines 4-5.

Claim objections under 37 C.F.R. § 1.126

Misnumbered claims pointed out by the Office action have been renumbered claims 25 and 26. Therefore, Applicants submit that the objections have been overcome and request reconsideration and withdrawal of the objection under 37 C.F.R. §1.126.

Rejections under 35 U.S.C. § 112, Second Paragraph

The Office action rejects claims 1-26 under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

First, the Office action rejects the use of parenthetical inclusions throughout the claims. These parenthetical inclusions and resultant abbreviations have been removed from all claims except claim 9 and new claim 38. Applicants submit that the use of parenthetical abbreviations should be permitted in claims 9 and 38 so that further dependent claims 10 and 39 are more reader-friendly. Applicants submit that use of these abbreviations neither limits nor expands the preceding terms. The parenthetical abbreviations are exactly the same as preceding terms and are provided for further reference in later claims. Therefore, Applicants request reconsideration and withdrawal of rejections of claims 1-26 based on this ground.

Second, the Office action rejects Applicants' use of the term "calcium" in the claims. Applicants have amended the appropriate claims to recite "calcium ion" instead, as the Office action suggests. Applicants point to various places in the application to support the amendment, for example, at page 3, line 30; at page 4, line 24; at page 5, line 9; and page 15, line 28. Therefore, Applicants respectfully request reconsideration and withdrawal of rejections of claims 1-26 based on this ground.

The Office action also rejects claims 25 and 26 for indefiniteness and has asked applicants to clarify what "100% protein S" and "40-50% protein S" mean. Applicants have amended claims 25 and 26 to recite "100 % protein S activity" and "40-50% protein S activity," respectively. Applicants submit that these amendments, supported at page 7, lines 9-11 of the specification, clarify what Applicants intend to claim as the invention. Therefore, Applicants respectfully request reconsideration and withdrawal of rejections of claims 25 and 26 based on this ground.

The Office action also rejects claim 8 asserting that "synthetic" is not a term of art with a consistent interpretation. Applicants respectfully the rejection. Applicants submit that "synthetic" is not ambiguous and point to page 9, lines 8-9 of the application which state that "[s]ynthetic phospholipids may be prepared by organic synthesis using standard methods." Furthermore, the specification states that the phospholipids may be "synthetic or purified (e.g. from plant or animal sources)" on page 6, line 16. Applicants submit that one skilled in the art would understand, from reading the Application, that synthetic phospholipids are those phospholipids organically synthesized rather than those purified from plant or animal sources. Therefore, Applicants request reconsideration and withdrawal of this rejection of claim 8.

Rejections under 35 U.S.C. § 102(b) over Preda

Claims 1-4, 14, and 21-24 are rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,147,805 to Preda *et al.* (hereinafter "Preda"). Among the claims at issue, four are independent claims: 1, 3, 23, and 24. Applicants respectfully traverse the rejections to the extent they are maintained over claims as amended.

Preda does not teach or suggest all the elements and limitations of the amended claims. Claims 1 and 3 both have been amended to recite use of "recombinant tissue factor" during the mixing step. Claim 24 has been amended to recite "synthetic phospholipid" as part of the claimed kit. According to the present invention, using recombinant tissue factor and/or synthetic phospholipid instead of tissue factor and/or phospholipid from crude extracts is advantageous in avoiding lot to lot variation in the sensitivity of the claimed protein S activity assay, and in avoiding contamination. *See* Application, page 5, lines 10-15; and page 8, lines 5-7. Preda does not describe or suggest the use of recombinant tissue factor or synthetic phospholipid, and therefore, does not anticipate any of amended claims 1, 3, and 24.

Claim 23 recites a kit that includes activated protein C as a component. According to the present invention, using exogenous protein C that has been activated takes another variable out of the assay, and also eliminates the time-consuming step of waiting for endogenous protein C to become activated. *See* Application, page 8, lines 10-13. Preda, in contrast, does not teach a kit with already activated protein C as a component, and therefore, does not anticipate claim 23.

At least for these reasons, Applicants respectfully submit that Preda does not teach or suggest each and every element of amended claims 1, 3, 23, and 24, and their dependent claims (i.e., claims 4, 14, and 21). Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 103(a) over Preda in view of Kraus

Claims 5, 7, 15, and 20 are rejected under 35 U.S.C. § 103(a) over Preda in view of U.S. Patent No. 5,726,028 to Kraus (hereinafter "Kraus"). These claims each depend from amended claims 1 or 3. Claim 5 has been cancelled. Applicants respectfully traverse the rejections to the extent they are maintained over the claims as amended.

The proper standard for evaluating obviousness requires a determination of (1) whether prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re Vaeck,* 947 F.2d 288, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and reasonable expectation of success must be found in the prior art, not in the Applicants' disclosure. *See id* (citing *In re Dow Chemical Co.* 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988)). Finally, 35 U.S.C. § 103 requires that the suggestion or incentive to combine prior art references must be derived from the teachings of the references. *See ACS Hosp. Systems, Inc. v. Montefiore Hosp.* 732 F.2d 1572, 1577, 21 U.S.P.Q. 929, 933 (Fed. Cir. 1984).

Applicants submit that Kraus specifically teaches away from combining with Preda. For its assay, Kraus describers that "[i]n contrast to earlier methods for protein C or protein S determination, the sample is not mixed with a corresponding deficient plasma so that only the factors in the sample itself are included in the determination." *See* Kraus, col. 3, lns. 44-47. In contrast, in Preda's assay, the test sample *is* mixed with such "corresponding deficient plasma," in this case, protein S deficient plasma. *See* Preda, col. 3, lns. 44-46; and col. 3, lns. 18-20. Consequently, a person skilled in the art, after reading Kraus, is specifically taught away from looking to assays that use protein S deficient plasma such as that of Preda.

At least for these reasons, Applicants respectfully request the reconsideration and withdrawal of rejections of amended claims 7, 15, and 20.

Rejections under 35 U.S.C. § 103(a) over Preda in view of Novy or Hawkins

Claims 6, 8, 9 and 10 are rejected under 35 U.S.C. 103(a) over Preda and further in view of US Patent No. 5,858,724 to Novy, Jr. *et al.* (hereinafter "Novy") or PCT Application WO 93/07492 by Hawkins *et al.* (hereinafter "Hawkins"). These claims each depend from amended claims 1 or 3. Applicants respectfully traverse the rejections to the extent they are maintained over the claims as amended.

Preda in view of Novy

Preda does not teach recombinant rabbit tissue factor as required by claim 6, however, the Office action states that Novy describes use of recombinant rabbit tissue factor in clotting assays. Applicants submit that this teaching of Novy should not be combined with Preda because Preda specifically teaches away from the use of rabbit tissue factor in a protein S assay. The following paragraph from Preda indicates that rabbit tissue factor (thromboplastin) is undesirable in a protein S assay:

> " It should be noted that the use of bovine thromboplastin with added calcium as proposed by the invention results in an analysis method which is surprisingly sensitive compared with the use of thromboplastin of other origin, such as *human* or *rabbit*. In this respect, the PT variations obtained using bovine thromboplastin with added calcium, when measured for example between the PTs obtained with the end 0% and 100% standards, are approximately 50 seconds. Using thromboplastin of other origin, the corresponding PT variations are only a fraction of this time, for example, just a few seconds. The greater sensitivity and repeatability of the method of the invention are therefore apparent when *bovine* thromboplastin with added calcium is used." (emphasis added) (*see* Preda, col. 3, ln. 58 – col. 4, ln. 3; *see also* FIG. 1.)

This statement specifically teaches that bovine tissue factor is more sensitive than its rabbit counterpart in a protein S assay. And because Novy's teaching regarding rabbit tissue factor is limited to a Factor VII assay, one skilled in the art, mindful of variations within different assays, would have no reasonable expectation of success in attempting to switch the bovine tissue factor in Preda with rabbit tissue factor.

Claim 8 has been amended to depend from claim 6, and therefore, is patentable over Preda in view of Novy at least for the above reasons. Claims 9 and 10 both recite three specific components of phospholipids that are not described in Preda or Novy. At least for these reasons, Applicants submit that claims 6, 8, 9 and 10 are nonobvious over Preda and Novy, and respectfully request the reconsideration and withdrawal of the rejections at issue.

Preda in view of Hawkins

Preda does not teach or suggest use of recombinant tissue factor as required by amended claims 1 and 3. Hawkins, however, describes a reagent that includes recombinant human tissue factor. As the above quoted text from Preda makes clear, however, human tissue factor is undesirable in Preda's assay. And because Hawkins is completely void of any teaching on specific assay methods, there is no motivation that overcomes the teach-away already in Preda.

Put in a slightly different way, Hawkins describes a reagent for coagulation assays without providing reasons or evidence that such reagent should replace the reagent already being used in Preda's protein S assay. Specifically, the assay performed by Hawkins uses a control reagent containing rabbit tissue factor. *See* Hawkins, page 14, lns. 19-21. This comparison between rabbit and human tissue factors does not provide any evidence that the bovine tissue factor favored by Preda should be replaced, as Preda already teaches that both the rabbit and human tissue factors are not desirable in its assay. Accordingly, Hawkins at best provides the skilled artisan with a mere invitation to experiment.

At least for these reasons, Applicants submit that claims 6, 8, 9, and 10, which depend from amended claims 1 or 3, are patentable over Preda in view of Hawkins, and respectfully request the reconsideration and withdrawal of the rejections at issue.

Rejections under 35 U.S.C. § 103(a) over Preda

Claims 11, 12, 16-19, 25, and 26 are rejected under 35 U.S.C. § 103(a) over Preda. Claims 16-19 have been canceled without prejudice. The remaining claims depend from amended claims 1, 23, or 24. As described above, amended claims 1, 23, or 24 are patentable over Preda. Therefore, Applicants respectfully request the reconsideration and withdrawal of the rejections of claims 11, 12, 25, and 26 under 35 U.S.C. § 103(a).

Rejection under 35 U.S.C. § 103(a) over Preda in view of Madden

Claim 13 is rejected under 35 U.S.C. § 103(a) over Preda in view of a publication in *Thrombosis Research*, (57): 425-35 by Madden *et al.* (hereinafter "Madden"). This claim depends from amended claim 1. Applicants traverse the rejection to the extent it is maintained over the claim as amended.

Madden does not teach or suggest the use of recombinant tissue factor. Accordingly, even if Madden is combined with Preda, all the limitations recited in amended claim 1 are not taught or suggested by Preda in view of Madden. At least for this reason, Applicants submit that amended claim 13 is patentable over Preda in view of Madden, and respectfully request the reconsideration and withdrawal of the rejection at issue.

New Claims

Applicants present new claims 27-51 for consideration by the Examiner, with claims 30, 33, and 47 being independent claims. Applicants respectfully submit that these claims are patentable over the art cited in the Office action.

CONCLUSION

In view of the amendments and remarks in this paper, Applicants respectfully request that all the outstanding objections and rejections be reconsidered and withdrawn. Applicants respectfully urge that all claims are in condition for allowance and request prompt and favorable action on the instant application. If the Examiner believe that a telephonic interview with the undersigned would expedite prosecution of this application, the Examiner is cordially invited to telephone the undersigned at (617) 248-7808.

Respectfully submitted,

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Reg. No. Limited Recognition

Duan Wu
Attorney for the Applicants
Testa, Hurwitz, & Thibeault, LLP
High Street Tower
125 High Street
Boston, Massachusetts 02110

Tel. No.: (617) 248-7808
Fax No.: (617) 248-7100